Different Relationship Between Anthropometric Markers and Umbilical Cord Plasma Leptin in Asian and Caucasian Neonates

LOUISA P.K. YEUNG, ALFRED C.K. WONG, XIAOHUI WANG, CARL L. BIRMINGHAM,
SABRINA LEWICKA, AND JEAN-PIERRE CHANOINE

*Endocrinology and Diabetes Unit, British Columbia's Children's Hospital, Vancouver BC V6H 3V4,
Canada [L.P.K.Y., A.C.K.W., X.W., J.-P. C.]; Eating Disorders Clinic, St-Paul's Hospital, Vancouver BC
V6Z 1Y6, Canada [C.L.B.]; Department of Pharmacology, University of Heidelberg, 69120 Heidelberg,
Germany [S.L.]*

ABSTRACT

The leptin to fat ratio early in life could contribute to fixing the set point of leptin feedback at the hypothalamic level. Subjects from Asian and Caucasian ethnicities differ in body composition. We tested the hypothesis that anthropometric markers and their relationship to umbilical cord leptin, cortisol and cortisone, DHEAs and oestriol differed between Caucasians and Asians at birth. Birthweight, length, arm, calf and abdominal circumferences, scapular, triceps, quadriceps and abdominal skinfolds were measured in 180 healthy, full-term newborns of Asian and Caucasian ethnicities. Leptin and steroid hormone concentrations were determined in umbilical cord plasma. There was a significant difference in the slope of the regression between leptin and birthweight ($p = 0.03$) and calf circumference ($p = 0.05$) between male Caucasian and Asian neonates. In contrast, in female neonates, there was no significant difference ($p = 0.099$ and $p = 0.07$ for birthweight and calf circumference, respectively). In addition, while the slopes of the regression plots were not affected by gender in Asian newborns, there was a significant difference between male and female Caucasian newborns ($p = 0.006$ and $p = 0.002$ for birthweight and calf circumference, respectively). There was no significant correlation between cord leptin concentrations or anthropometric markers and steroid hormone concentrations. In conclusion, gender and ethnic differences in the relationship between leptin and anthropometric markers are detectable at birth between Asians and Caucasians, two ethnic groups that have been demonstrated to have different body compositions later in life. This may represent the first clinical evidence of a difference in leptin regulation between these two ethnic groups. (*Pediatr Res* **53:** 1019–1024, 2003)

Abbreviations
BMI, body mass index
DHEAs, dehydroepiandrosterone sulfate

Leptin is a protein secreted mainly by the adipocyte in proportion to fat mass (1). An important role for leptin in humans is to inform the hypothalamus about the status of body-fat stores (2). Accordingly, a good correlation between leptin and body weight or fat mass has been repeatedly observed in adults (3) and infants (4–10). However, there is a wide dispersion in leptin concentrations for a given fat mass suggesting a variability in the relationship between leptin and body fat. The cause of this variability is largely unknown.

It has been suggested that programming of the hypothalamic regulatory mechanisms may play a role in the regulation of body fatness in adulthood (11–12) and Singhal *et al.* (13) recently postulated that early determinants of the leptin to fat ratio could contribute to fixing the set point of leptin feedback at the hypothalamic level. A better understanding of the factors driving the relationship between leptin and body composition early in life is, therefore, important.

A potential source of variation in serum leptin concentrations is body-fat distribution (14–15). Differences in body fat distribution have been identified between subjects from different ethnicities, including between Asians and Caucasians. Deurenberg *et al.* (16) found that for a given body mass index (BMI), adults from Caucasian ethnicity had a lower percentage of body fat compared with adults from Chinese ethnicity. Wang *et al.* (17) observed that healthy Asian adults have lower BMIs but a higher percent of body fat compared with Caucasian subjects. Malina *et al.* (18) observed that Asian adolescent girls had more trunk s.c. adipose tissue compared with Caucasians. Recently, He *et al.* (19) showed that a decrease in the extremity skinfold thickness was already evident during the prepubertal period in Asian compared with Caucasian girls.

Whether differences in body composition are present between Chinese and Caucasian subjects at birth or develop with time is unknown.

Another potential source of variability in leptin concentrations is the hormonal environment. For instance, the higher serum leptin concentrations observed in female compared with male subjects (20) as early as during the neonatal period (4, 9) are not only explained by differences in body composition, but also by differences in sex steroids (1, 21). Cortisol is another steroid hormone that has been shown to increase leptin secretion *in vitro* and *in vivo* (22, 23). Of interest for the present study, a positive correlation between leptin and cortisol umbilical cord-blood concentrations has been reported by Maffeis *et al.* (9), raising the possibility that endogenous cortisol secretion could stimulate leptin secretion in the perinatal period.

We hypothesized that differences in body fat distribution are already present in Caucasian and Chinese neonates, and that the relationship between umbilical cord leptin concentrations and body composition is different in these two ethnic groups. The primary goal of the present study was to assess the relationship between leptin and height, weight and anthropometric measures of fat distribution in healthy neonates from Caucasian and Asian origin born in Vancouver, British Columbia. The secondary objective was to determine whether the umbilical cord concentrations of cortisol, cortisone, oestriol and DHEAs, which could potentially differ in Asian and Caucasian newborns, would explain some of the variability in neonatal leptin concentrations that we expected to find in Caucasian and Asian newborns.

METHODS

Subjects. We prospectively studied 180 healthy full-term newborns divided into four groups of 45 according to gender (male or female) and ethnicity (Caucasian or Asian). All newborns were born at Children's and Women's Hospital of British Columbia over a 6-month period and had both parents and all grandparents of the same ethnicity according to the information volunteered by the mother. "Caucasian" origin corresponds to Anglo-European descent. "Asian" origin refers to families of Chinese descent, mainly from Hong Kong, Taiwan or mainland China. The study was approved by the Ethics Committee of the University of British Columbia and written informed consent was obtained from all mothers after the study was explained to them by the examiner.

Demographic data. Maternal age and gestational age (calculated according to the date of the last menstrual period or, if unknown, to the ultrasound results) were obtained from the medical record. The mother was asked about her smoking and drinking habits, length of residence in Canada and was questioned about the highest education level she achieved and the present occupation of both parents. Data regarding parental education were collected as middle school, high school, college, university, and postuniversity as proposed by Duncan *et al.* (24). For analytical purposes, education was defined as presecondary or postsecondary. Occupational categories in-

cluded operative, crafts, clerical (manual/nonmanual), service and manager.

Anthropometric characteristics. Birthweight and length were recorded at birth by the attending nurse. All other anthropometric determinations were performed within the first 24 h of life by a single examiner (L.P.K.Y). Scapular, quadriceps (mid-leg), triceps (mid-arm), and abdominal skinfolds were measured using a caliper (precision of 0.2 mm). Mid-arm, mid-calf, and abdominal (at the umbilicus) circumferences were measured using a measuring tape (precision of 1 mm). The intra-observer coefficient of variation was 0.5%.

Venous cord plasma. Cord blood was collected from the umbilical vein on EDTA, kept at 4°C for one to twenty-four hours before being centrifuged and stored at −80°C. Leptin (Linco, St-Charles, MO, U.S.A.; intra- and inter-assay coefficients of variation [CV] < 7.5% and < 8.9%, respectively) and dehydroepiandrosterone sulfate (DHEAs) (Diagnostic Products Corporation, Los Angeles, CA, U.S.A., intra- and inter-assay CV 4.4–5.3% and 6.3–8.1%) were measured by RIA (RIA) without extraction. Cortisone was measured by RIA after chloroform extraction as described by Weber *et al.* (25).

Unconjugated oestriol (intra- and inter-assay CV 1.8–2.5% and 3.4–4.7%, respectively) and cortisol (intra- and inter-assay CV < 6.7% and < 7.9%, respectively) concentrations were determined in simplicate by chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA, U.S.A.).

Statistical methods. Values are expressed as mean ± SD, except when noted. Sample size was determined based on the ability to detect a 25% difference in r^2 (r = relationship between cord leptin and birthweight in neonates of Caucasian and Asian ethnicities) with $\alpha = 0.05$ and $\beta = 0.80$, assuming an r value of 0.50 for the correlation between birthweight and leptin concentrations (4, 5).

The differences in baseline characteristics (gestational age, maternal age, length of stay in Canada and time of examination) were examined in a two-way (ethnicity and gender) analysis of variance. The differences in anthropometric measures and cord plasma hormonal concentrations (after log transformation as appropriate) were examined using a two-way analysis of covariance, with socio-economic status of the parents and birthweight of the newborns as covariates where appropriate. The differences in parental education and occupation were analyzed by χ^2 and Fisher's exact tests, respectively. A multiple linear regression model (using all 180 subjects) was used to investigate the nature of the relationship between cord plasma leptin concentrations and each of the anthropometric measures among the Caucasian and Asian female and male newborns, with logarithm of leptin as dependent variable, and anthropometric measures, ethnicity and gender as independent variables. Similarity of regression slopes among the subgroups was examined by the significance of the 3-way interaction between anthropometric measure, ethnicity and gender variables. Data were analyzed by using SAS software version 8.2 (SAS Institute Inc. Cary, NC, U.S.A.), with $p < 0.05$ as the significance level.

RESULTS

Demographic data. Table 1 describes the characteristics of the Caucasian and Asian neonates and their parents. There was no significant difference in maternal age and length of time after delivery that anthropometric measurements were performed. Gestational age was marginally but significantly smaller in Asian compared with Caucasian neonates. One Asian and eight Caucasian mothers smoked to some degree during pregnancy, and one mother in each ethnic group had drunk some alcohol during pregnancy. Removing these data from analysis did not influence the results.

In keeping with their recent history of immigration to British Columbia, length of stay in Canada was significantly shorter for Asian than for Caucasian parents ($p < 0.0001$). Asian fathers ($p = 0.02$) and mothers ($p = 0.04$) were significantly less likely to have received postsecondary education compared with their Caucasian counterparts. Accordingly, Caucasian fathers ($p = 0.07$) and mothers ($p < 0.0001$) had a higher employment level compared with their Asian counterparts, although the difference was only significant for mothers.

Anthropometric data. Table 2 describes the anthropometric characteristics of the four groups under study. Birthweight, length, arm circumference and triceps skinfold were all significantly affected by ethnicity, with Caucasian newborns having greater measurements than Asian newborns. Birthweight, length, arm circumference, and all skinfold determinations were significantly affected by gender, with male newborns having greater measures than female newborns. Abdomen circumference among the male newborns was found to be greater in Caucasian newborns ($p = 0.004$), but there was no evidence that the difference in ethnicity exists among the female newborns ($p = 0.54$). Similarly, within the Asian neonates, this measure was slightly greater in the male newborns ($p = 0.02$), but it was comparable between the male and female among the Caucasian newborns ($p = 0.97$).

Leptin and anthropometric data. Leptin concentrations were significantly higher in Asian and Caucasian female compared with male neonates, even after adjusting for birthweight (Table 3). Leptin concentrations were not affected by ethnicity.

The correlation between cord leptin concentration and anthropometric measures in each of the four sub-groups is presented in Table 4. To further investigate the effect of gender and ethnicity on the relationship between cord leptin concentration and each of the anthropometric measures, we fitted a multiple linear regression model and found that the relationship between leptin concentrations and several anthropometric determinations was significantly affected by gender and ethnicity. This was the case for the relationship between leptin and birthweight ($p = 0.009$) and calf circumference ($p = 0.009$). The slopes of the regressions were significantly different between Asians and Caucasians in male ($p = 0.03$ and $p = 0.05$ for birthweight and calf circumference, respectively) but not in female newborns ($p = 0.099$ and $p = 0.07$ for birthweight and calf circumference, respectively). In addition, while the slopes

Table 1. *Characteristics of the Asian and Caucasian neonates and their parents*

	Male		Female		
	Asian	Caucasian	Asian	Caucasian	2-way ANOVA
Gestational age (wk)	39.3 (1.2)	39.4 (1.0)	39.1 (1.1)	39.7 (1.1)	Race ($p = 0.03$)
Maternal age (y)	30.9 (4.2)	31.4 (4.6)	32.1 (5.0)	32.7 (4.9)	NS
Residence in Canada (y)	11.2 (10.4)	27.8 (9.6)	10.1 (9.1)	27.9 (12.4)	Race ($p < 0.0001$)
Time of exam (h after birth)	14.0 (7.4)	14.6 (8.1)	14.6 (6.7)	11.5 (7.2)	NS
Mean (SD)					

Table 2. *Anthropometric measurements of the Asian and Caucasian newborns*

	Male		Female		
	Asian	Caucasian	Asian	Caucasian	2-way ANCOVA
Birth weight (g)*	3325 (381)	3593 (436)	3179 (342)	3517 (367)	Race ($p < 0.0001$) Sex ($p = 0.06$)
Length (cm)*	51.4 (1.9)	52.5 (2.3)	50.7 (2.0)	51.5 (2.2)	Race ($p = 0.006$) Sex ($p = 0.01$)
BMI (kg/m^2)*	12.6 (1.2)	13.0 (1.2)	12.3 (0.9)	13.3 (1.1)	NS
Circumference (cm)†					
Arm	10.7 (0.8)	11.0 (0.8)	10.6 (0.8)	11.0 (0.8)	Race ($p = 0.028$) Sex ($p = 0.0002$)
Calf	11.8 (0.8)	12.2 (1.0)	11.5 (0.7)	12.1 (0.8)	NS
Abdomen	31.2 (1.7)	33.2 (2.6)	31.4 (1.8)	32.9 (1.8)	Race × Sex ($p = 0.049$)
Skinfold (mm)†					
Triceps	5.3 (1.0)	5.5 (1.0)	5.7 (0.8)	5.8 (1.2)	Race ($p = 0.027$) Sex ($p = 0.0001$)
Quadriceps	5.6 (1.0)	6.0 (1.1)	6.1 (0.8)	6.8 (1.2)	Sex ($p < 0.0001$)
Scapula	4.4 (0.9)	4.6 (1.0)	4.6 (1.0)	4.9 (1.0)	Sex ($p = 0.0057$)
Abdomen	3.3 (0.4)	3.3 (0.6)	3.4 (0.5)	3.5 (0.6)	Sex ($p = 0.022$)
Mean (SD)					

* Adjusted for parents' education.

† Adjusted for birthweight.

Table 3. *Cord blood hormonal concentrations in male and female neonates from Asian and Caucasian groups*

	Male		Female		
	Asian	Caucasian	Asian	Caucasian	2-way ANCOVA
Leptin* (ng/ml)	7.0 (4.9)	7.4 (4.4)	8.9 (5.4)	14.1 (11.9)	Sex ($p < 0.0001$)
Cortisol* (nmol/L)	593 (331)	587 (314)	618 (335)	519 (312)	NS
Cortisone (nmol/L)	330 (86)	305 (100)	310 (72)	291 (89)	NS
DHEAs (μmol/L)	6.1 (2.2)	4.7 (1.7)	7.2 (3.5)	4.7 (1.4)	Race ($p < 0.0001$)
Estriol* (nmol/L)	274 (132)	242 (134)	295 (126)	224 (83)	Race ($p = 0.0047$)

* Variable has been log-transformed for the analysis.

Mean (SD).

Conversion: Cortisol: 1 μg/dl = 27.6 nmol/l, Cortisone: 1 μg/dl = 27.7 nmol/l, DHEAs: 1 μg/dl = 25.6 nmol/l, Estriol: 1 μg/dl = 34.7 nmol/l.

Table 4. *Correlation between cord leptin concentrations and anthropometric measures in each of the sub-groups of Asian and Caucasian neonates*

	Male		Female	
	Asian	Caucasian	Asian	Caucasian
Birthweight	0.51†	0.48†	0.47*	0.58‡
Length	0.36*	0.23	0.28	0.18
Body Mass Index	0.33*	0.38*	0.33*	0.56‡
Circumference				
Arm	0.51†	0.62‡	0.60‡	0.51†
Calf	0.46*	0.47*	0.39*	0.65‡
Abdomen	0.32*	0.46*	0.29	0.45*
Skinfold				
Triceps	0.48†	0.57‡	0.50†	0.49†
Scapula	0.53†	0.42*	0.46*	0.54†
Quadriceps	0.50†	0.53†	0.33*	0.50†
Abdomen	0.33*	0.34*	0.30*	0.38*

r, Spearman coefficient of correlation.

* $p < 0.05$; † $p < 0.001$; ‡ $p < 0.0001$.

of the regressions were not affected by gender in Asian newborns, they were significantly different in male and female Caucasian newborns ($p = 0.006$ and $p = 0.002$ for birthweight and calf circumference, respectively) (Fig. 1).

Steroid hormone data. Plasma cortisol, cortisone (Table 3) and cortisol/cortisone ratios (data not shown) were similar in all four groups. In contrast, DHEAs concentrations were significantly higher in Asian male (+30%) and female (+54%) neonates compared with their Caucasian counterparts. The same trend was observed with oestriol although the difference was only significant in male newborns. There was no significant correlation between steroid hormones and leptin or any of the anthropometric measures.

DISCUSSION

In this study, we demonstrate for the first time that differences in body-fat distribution between Asians and Caucasians are already present at the time of birth and that the relationship between anthropometric measurements and umbilical cord leptin concentrations is affected by ethnicity and the sex of the infant.

Umbilical cord leptin could potentially originate from the fetal adipose tissue or from the placenta. Recent evidence suggests that the fetal adipocyte is the main determinant of circulating fetal leptin (26, 27). In contrast, while the placenta synthesizes leptin very actively (28), perfusion studies of human placentas have shown that the bulk of placental leptin is secreted into the maternal circulation (29).

In male newborns, absolute and relative (after normalization for birthweight) leptin concentrations are similar in Asians and Caucasians but the slope of the regression between leptin (after log transformation) and birthweight (and calf circumference) is different. Changes in birthweight of 500 g and 1 kg around the mean are associated with 30% and 70% differences in leptin concentrations, respectively, between Caucasian and Asian newborns. There is no significant difference in the relationship between leptin and other anthropometric markers. As calf circumference and birthweight are two of the best single anthropometric variables for the estimation of total body fat measured by total-body electrical conductivity in the neonate (30), our results suggest that we are indeed observing differences in the relationship between leptin and fat mass in these two groups. The cause of this difference is presently unclear. Conceptually, higher plasma leptin concentrations for a given body weight could be due to a greater number of adipocytes or to a higher quantity of leptin secreted per adipocyte. There are to our knowledge no data available on the characteristics of adipose tissue according to ethnicity.

In female neonates, there was no significant difference in the relationship between leptin and anthropometry in Asians and Caucasians. Whether a difference in the relationship between leptin and anthropometry between the sexes is also present later in life between Asians and Caucasians is not known but differences in body composition according to sex and ethnicity have been reported in Asian and Caucasian children by He *et al.* (19). For instance, extremity and gynecoid skinfold thickness are significantly greater in Caucasian compared with Asian girls, but not boys.

To our knowledge, there is only one other study comparing the growth of Asian and Caucasian infants. Tam *et al.* (31) compared the growth data of Chinese infants (obtained longitudinally during the first 2 years of life) to the NCHS reference data obtained mainly in Caucasian infants and children (32). Their results suggest that the BMIs of Chinese infants of both sexes increase more rapidly during the first seven to nine months of life compared with the NCHS data, mainly because of a more rapid weight gain. Whether this difference is due to genetic, nutritional or methodological factors (absence of a direct comparison between the two different groups) is unclear but these results suggest that fat accumulation during the first months of life may be different in Asian and Caucasian babies.

The comparison between the results we observe in newborns and published data in Asian and Caucasian adults is difficult. In addition to methodological differences, environmental factors
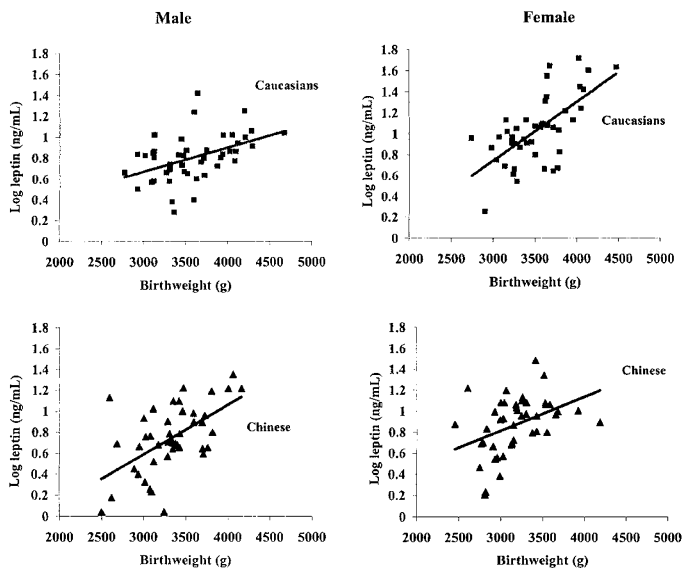
Figure 1. Relationship between cord log leptin concentration and birthweight in male (*left panel*) and female (*right panel*) newborns from Caucasian (*upper panel*) and Asian (*lower panel*) ethnicities. Male newborns: Caucasians: $y = 0.0002x + 0.07$; Asians: $y = 0.0005x - 0.83$; Female newborns: Caucasians: $y = 0.0006x - 0.94$; Asians: $y = 0.0003x - 0.15$; where $y =$ log leptin (ng/mL) and $x =$ birthweight (g).

are likely to influence body composition. Wang *et al.* (17) compared several anthropometric measurements between Caucasian and Asian (mostly Chinese) adults aged 18 to 94 years living in New York. Weight, height and BMI were lower in Asian compared with Caucasians. Similar to the results found in our study, circumference measurements at various body sites and triceps skinfold measurements were similar or significantly lower by four to 6% in Asian subjects. In contrast, subscapular and abdominal skinfold measurements that were larger in Asian adult subjects are found to be similar in our neonates.

The cause of the difference in leptin regulation observed in our neonates could be of genetic or environmental origin. Le Stunff *et al.* (33) have shown in obese Caucasian girls that the relationship between fat mass and leptin could be affected by a common polymorphism of the leptin promoter. Whether this applies to our population of neonates is presently unknown.

Another hypothesis is that steroid hormones, known to stimulate leptin production by the adipocyte, could affect the relationship between leptin and anthropometry in Asian and Caucasian neonates. We selected cortisol, cortisone, oestriol and DHEAs because the concentrations of these hormones, that reflect mainly the function of the placenta and/or the fetal compartment (34–36), could potentially be different in Asian and Caucasian neonates. The productions of cortisol (37), DHEAs (37) and oestriol (38) are inhibited by phytoestrogens, a main component of Asian diets and the umbilical cord concentrations of oestriol are different in Asian and Caucasian subjects (39). Our results do not, however, suggest that leptin concentrations or anthropometric measures can be predicted by umbilical cord concentrations of these steroid hormones.

We paid particular attention to cortisol and cortisone levels for the following reasons. First, cortisol is known to stimulate leptin secretion both *in vivo* and *in vitro* (22, 23). Second, the

activity of the placental enzyme 11 β-hydroxysteroid dehydrogenase (EC 1.1.1.146) that actively converts cortisol to cortisone near term has been shown to be positively correlated to birth weight (40) although this was not confirmed by Rogerson *et al.* (41). Finally, a relative deficiency in 11 β-hydroxysteroid dehydrogenase activity has been correlated with low birth weight, dyslipidemia, insulin resistance, and hypertension in adulthood (42, 43). In contrast to Maffeis *et al.* (9) and in agreement with Kirel *et al.* (44), we observed no correlation between cord cortisone or cortisol concentrations and birthweight.

Cord DHEAs concentrations specifically reflect the very active androgen production by the fetal adrenal (34) while cord oestriol concentrations reflect mainly the aromatization of 16 α hydroxy DHEAs by the placenta (35). We found no significant correlation between DHEAs or oestriol and leptin concentrations. However, DHEAs levels were higher in male and female Asian neonates compared with their Caucasian counterparts. In agreement with published data (39), cord oestriol concentrations were also higher in Asian neonates although the difference was only significant in the female group.

CONCLUSION

In conclusion, we have demonstrated that differences based both on sex and ethnicity in the relationship between leptin and anthropometric markers are detectable at birth between two ethnic groups that are known to have different body compositions in childhood, adolescence and adulthood. We propose that these findings may reflect a different leptin set-point for a given fat mass at the hypothalamic level and may play a role in the differences in fat distribution observed later in life.

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